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# Mitochondrial Dysfunction and Hematopoietic Impairment in Diabetes: The Oxidative Stress Connection

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## ABSTRACT

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, which leads to systemic complications. Among these, mitochondrial dysfunction plays a critical role in hematopoietic impairment, primarily through the induction of oxidative stress. The mitochondrial electron transport chain (ETC) is a significant source of reactive oxygen species (ROS) in diabetes, leading to oxidative damage in hematopoietic stem and progenitor cells (HSPCs). This review explores the intricate relationship between mitochondrial dysfunction, oxidative stress, and hematopoietic abnormalities in diabetes, discussing underlying molecular mechanisms and potential therapeutic strategies. We highlight the impact of excessive ROS production on hematopoietic homeostasis, including impaired erythropoiesis, leukopenia, and thrombocytopenia, which contribute to anemia, immune dysfunction, and increased risk of cardiovascular complications. Furthermore, we examine emerging therapeutic approaches aimed at mitigating oxidative stress and restoring mitochondrial function to improve hematopoietic health in diabetic patients.

**Keywords:** Mitochondrial dysfunction, Hematopoiesis, Diabetes, Oxidative stress, Reactive oxygen species, Hematopoietic stem cells, Antioxidant therapy

## INTRODUCTION

Diabetes mellitus (DM) is a major global public health concern, affecting millions of individuals across diverse populations[1–3]. This metabolic disorder is characterized by chronic hyperglycemia, resulting from either inadequate insulin production or insulin resistance, leading to widespread systemic complications[4–7]. Among the numerous organ systems affected, the hematopoietic system has garnered increasing attention due to its critical role in maintaining blood cell homeostasis and immune function[7–9]. The bone marrow, the primary site of hematopoiesis, harbors hematopoietic stem and progenitor cells (HSPCs), which are essential for replenishing blood cells throughout an individual's lifetime[10, 11]. In diabetic individuals, persistent hyperglycemia triggers a cascade of pathological changes, including inflammation, oxidative stress, and metabolic dysregulation, all of which contribute to hematopoietic impairment. One of the most significant consequences of DM is mitochondrial dysfunction, which generates excessive reactive oxygen species (ROS), leading to oxidative stress[12, 13]. The increased oxidative burden damages cellular components, impairs HSPC function, and disrupts hematopoietic balance, potentially predisposing individuals to hematologic abnormalities such as anemia, leukopenia, and compromised immune responses[13–15]. Mitochondrial dysfunction is a hallmark of diabetes-induced hematopoietic impairment, as mitochondria serve as the powerhouse of the cell, regulating energy metabolism and redox homeostasis. In the diabetic state, chronic hyperglycemia and insulin resistance lead to mitochondrial abnormalities, including impaired oxidative phosphorylation, mitochondrial DNA damage, and dysregulated mitophagy[13, 16, 17]. The excessive ROS generated as a byproduct of dysfunctional mitochondria exacerbates oxidative stress, further damaging HSPCs and disrupting their ability to self-renew and differentiate effectively. This oxidative burden also alters key signaling pathways, such as the nuclear factor erythroid 2-related factor 2 (NRF2) antioxidant response and the AMP-activated protein kinase (AMPK) pathway, both of which are crucial for maintaining cellular redox balance and metabolic stability[16]. Additionally, inflammatory mediators, such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), are upregulated in diabetes, compounding mitochondrial dysfunction and hematopoietic dysregulation. As a result, diabetic individuals often exhibit defective hematopoiesis, characterized by reduced regenerative capacity of HSPCs, increased apoptosis, and impaired differentiation into

functional blood cells. These changes not only compromise immune competence but also contribute to the heightened susceptibility of diabetic individuals to infections, anemia, and poor wound healing[18].
Given the detrimental effects of mitochondrial dysfunction and oxidative stress on hematopoiesis in diabetes, there is growing interest in identifying potential therapeutic interventions to mitigate these effects[19]. Strategies aimed at restoring mitochondrial function, enhancing antioxidant defenses, and modulating inflammatory pathways hold promise for improving hematopoietic outcomes in diabetic individuals. Pharmacological agents such as mitochondrial-targeted antioxidants (e.g., mitoquinone and MitoTEMPO) have demonstrated efficacy in reducing oxidative stress and preserving HSPC function[20]. Additionally, activators of NRF2 and AMPK, including natural compounds like resveratrol and metformin, have been explored for their ability to restore mitochondrial homeostasis and enhance hematopoietic function. Stem cell-based therapies, including the transplantation of healthy HSPCs and mesenchymal stem cells, are also being investigated as potential regenerative approaches to counteract diabetes-induced hematopoietic defects[21, 22]. Further research into the molecular mechanisms underlying mitochondrial dysfunction in diabetes and the development of targeted interventions will be essential for mitigating hematopoietic complications and improving overall health outcomes in diabetic individuals.



## Mitochondrial Dysfunction in Diabetes

Mitochondria, often referred to as the powerhouses of the cell, are indispensable for energy metabolism, primarily through the oxidative phosphorylation (OXPHOS) system[23]. This system facilitates ATP production by driving electron flow through the electron transport chain (ETC), culminating in oxidative phosphorylation. However, in diabetes, mitochondrial dysfunction emerges as a critical pathological feature, contributing to cellular and metabolic disturbances. One of the key impairments observed is the disruption of the ETC activity due to hyperglycemia[24]. Persistent high glucose levels drive excessive electron leakage within the ETC, leading to an overproduction of reactive oxygen species (ROS). This surge in ROS inflicts oxidative damage on mitochondrial components, including proteins, lipids, and mitochondrial DNA (mtDNA), ultimately impairing cellular respiration and ATP synthesis[25]. As oxidative stress escalates, it further exacerbates insulin resistance and β-cell dysfunction, hallmark features of both type 1 and type 2 diabetes. Consequently, the vicious cycle of mitochondrial damage and metabolic dysregulation perpetuates disease progression, underscoring the critical need to target mitochondrial health in diabetes management[12, 26, 27].
Mitochondrial DNA (mtDNA) damage represents another significant consequence of diabetes-induced oxidative stress. Unlike nuclear DNA, mtDNA is particularly vulnerable to oxidative modifications due to its close proximity to the ETC and lack of protective histones[28]. Persistent exposure to elevated ROS levels can result in mtDNA mutations and deletions, disrupting the expression of essential mitochondrial genes involved in energy metabolism. These genetic alterations compromise mitochondrial function, leading to impaired OXPHOS efficiency and further accumulation of dysfunctional mitochondria[28, 29]. The consequence of such dysfunction is a decline in ATP production, heightened apoptosis, and increased susceptibility to metabolic stress. Moreover, diabetes affects mitochondrial biogenesis, further impairing cellular adaptation to energy demands. The dysregulation of transcription factors such as peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) and nuclear respiratory factors (NRFs) diminishes mitochondrial turnover and exacerbates metabolic inflexibility[30]. In muscle and pancreatic β-cells, where energy metabolism is paramount, this mitochondrial impairment directly influences glucose homeostasis, insulin secretion, and peripheral tissue insulin sensitivity. As a result, restoring mitochondrial integrity emerges as a promising avenue for improving metabolic outcomes in diabetic patients[31].
Beyond mtDNA damage, diabetes disrupts mitochondrial dynamics, the tightly regulated balance between mitochondrial fission and fusion, essential for maintaining mitochondrial morphology and function. Under physiological conditions, fusion facilitates mitochondrial repair by allowing functional mitochondria to merge and compensate for damaged components, while fission ensures the removal of defective mitochondria through mitophagy [31, 32]. However, diabetes skews this balance, often favoring excessive fission over fusion, leading to fragmented and dysfunctional mitochondria [32]. This imbalance impairs mitochondrial networking, decreases ATP synthesis, and enhances susceptibility to apoptosis. Additionally, defective mitophagy, the selective degradation of damaged mitochondria, further exacerbates mitochondrial dysfunction in diabetes[32]. The impairment of mitophagy results in the accumulation of damaged mitochondria, increasing oxidative stress and perpetuating metabolic derangements. Dysfunctional mitophagy has been linked to β-cell failure and insulin resistance, reinforcing its role in diabetes pathophysiology. Given the critical involvement of mitochondrial quality control mechanisms in cellular energy homeostasis, therapeutic strategies aimed at modulating mitochondrial dynamics and enhancing mitophagy hold potential for mitigating diabetes-associated complications. Recent advancements in pharmacological agents and lifestyle interventions, such as exercise and caloric restriction, have shown promise in improving mitochondrial function and restoring metabolic balance. Thus, understanding and targeting mitochondrial dysfunction remains a cornerstone in developing novel therapeutic approaches for diabetes management.

## Oxidative Stress and Hematopoietic Impairment in Diabetes

Oxidative stress is a physiological condition characterized by an imbalance between the generation of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms[19, 27]. ROS are highly reactive molecules that can damage cellular components such as lipids, proteins, and DNA. Under normal conditions, ROS play a role in regulating various cellular processes. However, excessive production of ROS can overwhelm the body's defense systems, leading to cellular damage and dysfunction. In the context of diabetes, oxidative stress is exacerbated due to the chronic hyperglycemic state, which results in the overproduction of ROS. The elevated levels of ROS in diabetic individuals contribute significantly to the pathophysiology of various complications, particularly those affecting the hematopoietic system[17]. This imbalance plays a pivotal role in the dysfunction of blood cells, including erythrocytes, leukocytes, and platelets, which contributes to several systemic problems observed in diabetic patients.

One of the critical effects of oxidative stress in diabetes is its impact on erythropoiesis, the process of red blood cell production[33, 34]. Oxidative damage to hematopoietic cells, particularly in the bone marrow, can disrupt normal erythropoiesis, leading to a reduction in the number of functional red blood cells. This occurs due to two main mechanisms: decreased production of erythropoietin (EPO) and increased apoptosis of erythrocytes. EPO is a hormone that stimulates red blood cell production in the bone marrow. In the presence of excessive ROS, the production of EPO is impaired, reducing the ability of the body to generate new red blood cells[35]. Furthermore, oxidative stress accelerates the apoptosis of mature erythrocytes, shortening their lifespan and contributing to anemia, a common condition observed in diabetic individuals. Anemia in diabetes further exacerbates the already compromised oxygen delivery to tissues, leading to fatigue, weakness, and other complications associated with insufficient oxygenation of vital organs. In addition to impairing erythropoiesis, oxidative stress also leads to leukocyte dysfunction, affecting the immune system's ability to respond effectively to infections. White blood cells (leukocytes) are integral to the body's defense mechanisms, but ROS-induced damage to these cells can result in immune suppression[36]. ROS have been shown to alter the function and viability of leukocytes, leading to an impaired immune response. This dysfunction not only reduces the ability to fight infections but also increases susceptibility to opportunistic infections, which are more prevalent in individuals with diabetes. Moreover, oxidative stress can alter the signaling pathways within leukocytes, hindering their ability to migrate to sites of infection, phagocytose pathogens, and initiate an effective immune response[37]. The resultant immune suppression creates a vicious cycle where diabetic individuals are at a higher risk of infections, further complicating their clinical management and quality of life.

Finally, oxidative stress contributes to platelet dysfunction and thrombocytopenia, which increases the risk of thrombotic events in diabetic individuals. Platelets are critical for blood clotting, but excessive ROS can lead to platelet activation and aggregation, a process that plays a central role in the formation of blood clots. When oxidative stress causes platelet dysfunction, it promotes an abnormal increase in platelet aggregation, which can lead to the development of thrombi (blood clots). These thrombi can obstruct blood flow, increasing the risk of serious cardiovascular events such as stroke, myocardial infarction, and deep vein thrombosis. In addition to platelet activation, oxidative stress has been implicated in thrombocytopenia, a condition characterized by an abnormally low platelet count. The increased ROS can cause damage to platelets, leading to their premature destruction. Thrombocytopenia further complicates the risk of bleeding in diabetic individuals, creating a dual risk of both thrombosis and bleeding. Thus, the dysregulation of platelet function under oxidative stress significantly contributes to the increased morbidity and mortality associated with diabetes, particularly in cardiovascular and thrombotic complications.

In sum, oxidative stress in diabetes exerts profound effects on hematopoietic cells, leading to anemia, immune dysfunction, and platelet abnormalities. The imbalance between ROS production and antioxidant defenses accelerates the damage to red blood cells, white blood cells, and platelets, contributing to a variety of systemic complications. These effects highlight the importance of managing oxidative stress in diabetes, both to improve patient outcomes and to prevent the progression of associated complications. The increasing evidence of oxidative stress's role in the hematopoietic system underscores the need for therapeutic interventions aimed at reducing ROS levels or enhancing antioxidant defenses in diabetic individuals. By addressing oxidative stress, it may be possible to mitigate the hematopoietic dysfunctions and improve overall health outcomes for people living with diabetes.

## Molecular Mechanisms Linking Mitochondrial Dysfunction to Hematopoietic Impairment

Oxidative stress is a critical factor in the regulation of hematopoiesis, influencing hematopoietic stem and progenitor cell (HSPC) function. Several molecular pathways are implicated in mediating the effects of oxidative stress on hematopoietic cells. One of the most well-known pathways activated by oxidative stress is the NF-κB pathway, which plays a central role in immune and inflammatory responses [38]. Chronic oxidative stress can trigger NF-κB activation, which leads to the expression of pro-inflammatory cytokines, chemokines, and adhesion molecules. In the context of hematopoiesis, this inflammatory response can disrupt the normal function of HSPCs, leading to altered differentiation, proliferation, and survival of blood cells. In particular, oxidative

stress-induced NF-κB activation has been linked to the disruption of hematopoietic stem cell niches, which affects the maintenance and renewal of HSPCs. Moreover, this inflammatory environment can cause an imbalance in the hematopoietic compartment, leading to the development of hematological disorders such as anemia, myeloproliferative diseases, and leukemias. Therefore, targeting the NF-κB pathway may offer potential therapeutic strategies to counteract the detrimental effects of oxidative stress on hematopoiesis [39].



Another significant molecular pathway affected by oxidative stress is the p53-mediated apoptosis pathway. Reactive oxygen species (ROS), generated during oxidative stress, induce DNA damage in hematopoietic cells, which activates the tumor suppressor protein p53[39]. Once activated, p53 triggers a cascade of events that lead to cell cycle arrest and, if the damage is beyond repair, apoptosis. In the context of HSPCs, ROS-induced DNA damage and subsequent activation of p53 can promote the apoptosis of these critical stem cells, thereby impairing hematopoiesis[40]. This apoptotic response serves as a protective mechanism to eliminate damaged cells, but excessive or chronic activation of p53 in the face of persistent oxidative stress can lead to the depletion of HSPCs, hindering the regeneration and maintenance of the hematopoietic system. This dysregulation of p53-mediated apoptosis may contribute to hematopoietic failure, increased susceptibility to infections, and the development of blood disorders. Interestingly, the relationship between p53 and oxidative stress is bidirectional, as p53 also plays a role in modulating the oxidative stress response. Therefore, understanding the balance between p53-mediated apoptosis and cell survival in the presence of oxidative stress is critical for comprehending the impact of oxidative damage on hematopoiesis [40,41,42,43,44].

In addition to NF-κB activation and p53-mediated apoptosis, oxidative stress can also disrupt cellular antioxidant defense mechanisms, such as the Nrf2 signaling pathway. Nrf2 is a transcription factor that regulates the expression of various genes involved in antioxidant responses, detoxification, and cellular stress resistance. Under normal conditions, Nrf2 is activated in response to oxidative stress, leading to the upregulation of genes that protect cells from ROS-induced damage. However, in the presence of chronic oxidative stress, Nrf2 signaling can become impaired, reducing the cell's ability to defend against oxidative damage [45,46,47]. In hematopoietic cells, dysregulation of Nrf2 signaling compromises the cellular antioxidant defense mechanisms, making HSPCs more vulnerable to oxidative stress-induced damage. This reduction in cellular defense increases the risk of DNA damage, genomic instability, and cellular senescence, which can negatively impact hematopoiesis. Furthermore, the loss of Nrf2-mediated antioxidant responses has been implicated in various hematological diseases, including hematopoietic malignancies [45,46,47]. Restoring Nrf2 function or enhancing its antioxidant response could represent a potential therapeutic approach to protect hematopoietic cells from the harmful effects of oxidative stress. The ability of Nrf2 to maintain redox homeostasis in hematopoietic cells underscores its importance in safeguarding the integrity and function of HSPCs in the face of oxidative challenges. Furthermore, oxidative stress-induced disruption of mitochondrial function is a key factor affecting hematopoiesis, particularly in the context of metabolic diseases like diabetes. Mitochondria are essential for energy production and cellular metabolism, and their dysfunction can have detrimental effects on cell survival and function[45, 46, 47]. In HSPCs, mitochondrial biogenesis and function are critical for maintaining cellular homeostasis and promoting proper differentiation and self-renewal. Under conditions of oxidative stress, such as in diabetic environments, mitochondrial biogenesis can be impaired, leading to mitochondrial dysfunction and energy deficits. One of the key regulators of mitochondrial biogenesis is peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which orchestrates the expression of genes involved in mitochondrial function and energy metabolism. In diabetes, the downregulation of PGC-1α contributes to reduced mitochondrial biogenesis, compromising HSPC function. This disruption in mitochondrial dynamics not only impairs energy production but also exacerbates oxidative stress, creating a vicious cycle that further damages HSPCs. Consequently, the loss of mitochondrial function in HSPCs can lead to hematopoietic failure, impaired blood cell production, and an increased susceptibility to diseases such as anemia and myelodysplastic syndromes[47,48]. The therapeutic modulation of mitochondrial biogenesis, particularly by targeting PGC-1α, could offer a promising strategy to mitigate the effects of oxidative stress on hematopoiesis and improve the function of HSPCs in metabolic disorders like diabetes. Therefore, the intricate interplay between oxidative stress, mitochondrial dysfunction, and HSPC regulation is crucial for understanding how chronic diseases disrupt normal hematopoiesis.

## Potential Therapeutic Approaches

Restoring mitochondrial function and reducing oxidative stress may improve hematopoietic outcomes in diabetes. Potential strategies include:

**Antioxidant Therapies**: Supplementation with antioxidants such as N-acetylcysteine (NAC), resveratrol, and coenzyme Q10 may reduce oxidative damage.

**Mitochondrial Targeted Therapies**: Agents like MitoQ and SkQ1 selectively target mitochondrial ROS to protect hematopoietic cells.

**Metabolic Modulators**: Metformin and PGC-1α activators improve mitochondrial efficiency and reduce ROS production.

**Gene Therapy Approaches**: Targeting mitochondrial biogenesis and oxidative stress pathways using CRISPR-based strategies could provide long-term benefits.

## CONCLUSION

Mitochondrial dysfunction and oxidative stress play central roles in the hematopoietic impairments observed in diabetes. Understanding these mechanisms offers new avenues for therapeutic interventions aimed at mitigating oxidative damage and restoring hematopoietic function. Future research should focus on refining mitochondrial-targeted therapies to improve hematopoietic health in diabetic patients.



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